UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

008895

13 1991

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: 627. Pynamin Forte. Review of Rat Developmental Toxicity Tests: Range-Finding and Main Studies.

Tox. Chem. No. 025B
Project Nos. 1-2059 and 1-2064

TO: Richard King, PM Team # 72
Special Review and
Reregistration Division (H7508W)

FROM: Pamela M. Hurley, Toxicologist Pamela M. Hurley 12/2/91
Section I, Toxicology Branch I
Health Effects Division (H7509C)

THRU: Roger L. Gardner, Section Head Roger L. Gardner 12-3-91
Section I, Toxicology Branch I
Health Effects Division (H7509C) KB 12/11/91

Record No(s). S397616 and S397626

Background and Request:

In response to the Registration Standard on Allethrins, Sumitomo Chemical Company has submitted a developmental toxicity range-finding study and a full developmental toxicity study on rats with Pynamin Forte. The Toxicology Branch (TB-I) has been asked to review the submitted studies.

Toxicology Branch Response:

TB-I has reviewed the range-finding study and the full developmental toxicity study in rats on Pynamin Forte. The range-finding study is classified as Core Supplementary and the full study is classified as Core Guideline. The full study satisfies the regulatory requirement for a developmental toxicity study in rats on Technical Pynamin Forte. The following paragraphs are short summaries of the results of the studies.

Pynamin Forte was tested in a range-finding developmental toxicity study in rats at the following dose levels: 0, 50, 100, 200 and 300 mg/kg/day. The NOEL for maternal toxicity was close to 50 mg/kg/day and the LEL was 100 mg/kg/day (death [200 and 300 mg/kg/day], tremors, lost righting reflex, catalepsy, excess salivation, clonic convulsions, labored breathing, bradypnea and

1

Printed on Recycled Paper

decreased motor activity). There were no developmental effects. The developmental NOEL was 300 mg/kg/day (HDT).

Pynamin Forte was tested for potential to induce developmental toxicity in rats at the following dose levels: 0, 10, 30 and 100 mg/kg/day. The maternal NOEL was 30 mg/kg/day and the maternal LEL was 100 mg/kg/day (excess salivation and tremors and a decrease in mean body weight gain during days 6-9 of gestation when compared to the control group). The NOEL for developmental toxicity was 100 mg/kg/day (HDT).

Reviewed By: Pamela Hurley, Ph.D. Pamela M. Hurley 12/2/91
Section I, Tox. Branch (H7509C)
Secondary Reviewer: Roger L. Gardner, Head Roger Gardner 12-3-91
Section I, Tox. Branch (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Developmental Toxicity Range-Finding

SPECIES: Rats

TOX. CHEM. NO./CASWELL NO.: 025B

ACCESSION NUMBER/MRID NO.: 412258-02

TEST MATERIAL: Pynamin Forte

SYNONYMS: D-cis/trans allethrin

STUDY NUMBER(S): KT-91-0093

REPORT NUMBER: Argus Protocol 1119-004P

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Range-Finding Teratology Study in Rats

AUTHOR(S): A.M. Hoberman

REPORT ISSUED: 7/17/89

CONCLUSION: Pynamin Forte was tested in a range-finding developmental toxicity study in rats at the following dose levels: 0, 50, 100, 200 and 300 mg/kg/day. The NOEL for maternal toxicity was close to 50 mg/kg/day and the LEL was 100 mg/kg/day (death (200 and 300 mg/kg/day), tremors, lost righting reflex, catalepsy, excess salivation, clonic convulsions, labored breathing, bradypnea and decreased motor activity). There were no developmental effects. The developmental NOEL was 300 mg/kg/day (HDT).

Classification: Supplementary

Testing Guideline Satisfied: None

A. MATERIALS AND METHODS:

1. Test Compound(s)

Chemical Name: 36.5% allyl homolog of cinerin I and 55.5% other allethrin stereoisomers

Description: Amber colored liquid
Batch #(s), Other #(s): Lot 50310
Purity: 93.4%
Source: Sumitomo Chemical Company, Ltd.
Vehicle (if applicable): aqueous 0.5% (w/v) methylcellulose

2. Test Animals)

Species and Strain (sexes): Male and female Crl:COBS®CD®(SD)BR rats.
Age: 78 days (females)
Weight(s): 203-259 grams (females)
Source(s): Charles River Breeding Laboratories, Inc., Portage, Michigan

3. Study Design:

This study was designed to assess the developmental toxicity potential of Pynamin Forte when administered by gavage to rats on gestation days 6 through 15, inclusive, in order to identify dosage levels to be used in an expanded developmental toxicity study.

a. Mating:

Natural or artificial insemination? Natural
Describe technique used: Each female rat was placed in cohabitation for up to 3 days with a male rat and was examined daily for presence of spermatozoa in vaginal lavages or a copulatory plug. The day evidence of mating was found was designated as day 0 of presumed gestation.

b. Group Arrangement:

Test Group	Dosage (mg/kg/day)	Pynamin Forte Concentration (mg/ml)	Dosage Volume (ml/kg)	No. Assigned
I	0	0	5	8
II	50	10	5	8
III	100	20	5	8
IV	200	40	5	8
V	300	60	5	8

c. Dosing:

All doses were in a volume of 5 ml/kg of body weight/day. Dosing was based on daily gestation day body weight.

1) Basis For Selection of Dose Levels: Not stated, but this is a range-finding study being conducted in order to select dose levels for the main study.

2) Preparation: The appropriate amount of the test chemical was weighed out and a sufficient amount of vehicle was added to achieve a total volume of 30 ml. The container was capped, shaken and blended, allowed to stand to allow air bubbles to dissipate and stirred prior to dosing.

3) Frequency of Preparation: Daily.

4) Storage Conditions: The test substance was kept in a cool, dry, well ventilated area and protected from heat.

5) Stability Analyses: Stability of the test substance was on file with the Sponsor and was not provided in the report.

6) Homogeneity Analyses: Conducted on the lowest and highest concentrations used in the study, ranging from 2 mg/ml to 100 mg/ml. Samples were taken from the top, middle and bottom of the sample mixture.

7) Concentration Analyses: Duplicate 10 ml samples of each prepared batch were frozen immediately after the first day of preparation, and one 10 ml sample of each prepared batch was reserved on each of the last 4 days of the test substance preparation. The samples taken from each concentration prepared on the first day and the last day of dosage were sent frozen to Lancaster Laboratories, Lancaster, PA for analyses.

d. Maternal Examinations

1) Clinical Observations and Mortality: All female rats were observed for appearance, toxic effects, moribundity and/or mortality and general behavior at least twice daily during acclimation, cohabitation and early gestation (days 0-6) at at least four times daily during the dosage and postdosage periods of the study.

2) Body Weight Determinations: Maternal body weights were recorded twice prior to initiation of cohabitation, on day 0 of presumed gestation and then daily during the dosage and postdosage periods.

3) Food Consumption: Food consumption was recorded daily for each day of the dosing and postdosing periods (days 6 - 20 of presumed gestation).

4) Gross Necropsy:

Animals which died or were sacrificed in moribund condition prior to end of exposure period and were subjected to complete gross pathological examinations: All dams. The cause of death was recorded when possible. All gross lesions were preserved in formalin for possible future evaluation.

Animals sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All does. All gross lesions were preserved in formalin for possible future evaluation.

5) Uterine Examinations: The following observations were recorded:

Number of corpora lutea
Number of live fetuses
Number of dead fetuses
Early and late resorptions
Total implantations

e. Fetal Examinations:

The fetuses were examined in the following manner: The fetuses were removed from the uterus and individually identified by litter and uterine placement. Every fetus was sexed, weighed and examined for external abnormalities. Approximately one-half of the fetuses from each litter were preserved in alcohol, and the remaining fetuses were preserved in Bouin's solution.

f. Historical Control Data:

Historical control data were not provided to allow comparison with concurrent controls.

g. Statistical analysis:

The following statistical analysis methods were employed: parametric and nonparametric tests. These include Bartlett's (test for homogeneity of variance), analysis of variance (ANOVA - for homogeneous data), Dunnett's (if ANOVA significant), Kruskal-Wallis (nonparametric, not including proportion data, <= 75% ties), Dunn's test (if Kruskal-Wallis test is significant), Fisher's exact test for > 75% ties, variance test for homogeneity of the bionomial distribution (proportion data), analysis of covariance and covariance analyses t-test.

h. Compliance:

A signed Statement of Confidentiality Claim was provided (only on the basis of its falling within the scope of FIFRA). The document is considered to be confidential and trade secret information in all other countries and for all purposes other than those enunciated in FIFRA.

A signed Statement of compliance with EPA GLP's was provided.

B. RESULTS:

1. Dosage Preparation: For the 60 mg/ml level, the 2 samples were both 15% above the target concentration; for the 40 mg/ml level, one sample was 1.5% and the other sample was 8.8% above the target concentration; for the 20 mg/ml level, the samples were 12.0% and 4.0% above the target concentration and for the 10 mg/ml level, one sample was 0.1% below the target concentration and the other sample was 3.7% below the target concentration. The actual concentrations were acceptably close to the target concentrations.

Testing of the homogeneity samples resulted in an average relative standard deviation of 2.38% for the 2.0 mg/ml level, 5.5% for 3.0 mg/ml, 1.1% for 5.0 mg/ml, 8.56% for 60.0 mg/ml, 2.02% for 80.0 mg/ml and 1.03% for the 100 mg/ml level. The samples were acceptably homogeneous.

2. Maternal Toxicity:

a. Clinical Observations and Mortality: Two dams died in the 300 mg/kg/day group and one died in the 200 mg/kg/day group, both as a result of the effects of the test substance. One dam died in the 100 mg/kg/day group from an intubation error. No other deaths were observed. One 300 mg/kg/day animal died 2.5 hours after the first dose. Clinical observations for this female included tremors, lost righting reflex, catalepsy, excess salivation, clonic convulsions, labored breathing and bradypnea. This animal was identified as non-pregnant. The other 300 mg/kg/day dam died 2.5 hours after the second dose. Clinical observations for this dam included tremors, lost righting reflex and decreased motor activity. Its uterine contents consisted of 15 apparently normal embryos in situ. The 200 mg/kg/day dam died on

day 7 of presumed gestation, approximately 21 hours after the first dose. This rat had tremors. Its uterine contents consisted of 16 implantation sites with 16 apparently normal embryos in situ. The dam which died from an intubation accident also had clinical signs of toxicity (excess salivation and tremors). It also had 17 apparently normal developing embryos.

Clinical signs of toxicity were observed in all dose groups. These included: excess salivation ($p <= 0.05$ to $p <= 0.01$ at 50 mg/kg/day and above) and tremors ($p <= 0.01$ at 100 mg/kg/day and above). No other treatment-related clinical signs of toxicity were observed.

b. Body Weight Determinations: Decreases in body weight gain were observed in dams at 100 mg/kg/day and above during the first 3 days of treatment. Maternal body weight gain tended to be slightly depressed for the two highest dose levels throughout the rest of the dosing period. All treated groups had a slight rebound effect in body weight gain following the dosing period (gestation days 16-20). None of these effects were statistically significant when compared to control values.

The investigators supplied the following data:

Table I: Mean Body Weight Gains (Gm)[a]

Group:	Days 0 - 6	Days 6 - 9	Days 6 - 16	Days 16 - 20	Days 0 - 20
Control	33.2	11.8	56.4	114.4	147.6
50	33.9	10.0	54.8	115.6	151.5
100	32.2	8.7	56.1	120.4	154.6
200	31.5	9.6	55.7	122.7	153.3
300	32.0	7.0	52.4	119.2	149.0

a = Data extracted from (study or report number Argus 1119-004P and table 4)

c. Food Consumption: There was a decrease in food consumption during days 6-9 of gestation in all treated groups at 100 mg/kg/day and above. As with body weights, food consumption values tended to be lower than the controls group from days 6-16 for the treated groups 100 mg/kg/day and above. A small rebound effect occurred in all treated groups during the post-dosing period. None of the

changes in food consumption were statistically significant when compared to controls.

d. Gross Pathology: The only observation that was made on the dams and female that died due to exposure to the test material was a gas-filled gastrointestinal tract in one of the 300 mg/kg/day dams. No other treatment-related gross lesions were observed in any dose group. The dam that died due to an intubation accident had excess salivation, chromodacryorrhea and chromorrhinorrhea, as well as hemorrhagic lungs and a perforation in the esophagus with related abscess formation in the axillary musculature. Renal lesions were observed in 2 control rats. The right kidney and ureter in one dam was dilated, and the surface of the kidney had 2 pale areas that extended into the renal medulla. The other dam had an enlarged, pale left kidney containing 3 white foci that extended from the surface to the medulla, a moderately dilated pelvis that contained cloudy white fluid, and associated severe dilated of the left ureter.

e. Caesarean Section Observations: There were no treatment-related differences between the control and treated groups in the number and percentages of rats that were pregnant, the mean number of corpora lutea, implantations or implantation efficiencies, the number of live fetuses and resorptions, the litter sizes and the percentages of live male fetuses/litter. In addition, the incidences of dams with any resorptions were unaffected by administration of the test substance. The authors stated that the small non-dosage dependent increases ($p>0.05$) in fetal body weight in the 100, 200 and 300 mg/kg/day dose groups reflect the rebound effect on maternal body weight gain and feed consumption that occurred in dams in these dose groups during the postdosing period, days 16-20 of gestation. The following table summarizes the findings.

Table III: Cesarean Section observations[a]

Dose: mg/kg/day	0	50	100	200	300
#Animals Assigned	8	8	8	8	8
#Animals Mated/Inseminated	8	8	8	8	8
Pregnancy Rate (%)	8(100)	8(100)	8(100)	8(100)	6(75)
Maternal Wastage					
#Died	0	0	1	1	2
#Died/pregnant	0	0	1	1	1
#Non pregnant	0	0	0	0	1
#Aborted	0	0	0	0	0
#Premature Delivery	0	0	0	0	0
Corpora Lutea/dam	16.4	17.1	16.7	18.3	16.8
Implantations/Dam	14.8	15.1	15.7	15.7	15.8
Implantation Efficiency (%)[b]	91.6	89.2	94.1	88.1	90.2
Litter Size/Dam	13.8	13.9	14.3	15.1	14.6
Total Live Fetuses	110	111	100	106	73
Live Fetuses/Dam	13.8	13.9	14.3	15.1	14.6
Total Dead Fetuses	0	0	0	0	0
Dead Fetuses/Dam	0	0	0	0	0
Early Resorptions	8	9	10	4	2
per Dam	1.0	1.1	1.4	0.6	0.4
Late Resorptions	0	1	0	0	0
per Dam	0	0.1	0	0	0
Total Resorptions/Dam	1.0	1.2	1.4	0.6	0.4
Does With Any Resorptions (%)	4(50)	7(87.5)	5(71.4)	2(28.6)	1(20.0)
Does With All Conceptuses Resorbing (%)	0	0	0	0	0
Does With Viable Fetuses (%)	8(100)	8(100)	7(100)	7(100)	5(100)
Mean Fetal Weight (gm)	3.51	3.51	3.64	3.58	3.66
Sex Ratio (% Live Male) per Litter	48.3	48.2	48.9	52.9	50.8

[a] = Data extracted from (study or report number 1119-004P and tables 7 and 8).

[b] = Implantation efficiency is the number of implantation sites divided by the number of corpora lutea multiplied by 100.

3. Developmental Toxicity: No external alterations were observed in any of the treated or control groups.

Table IV: External Examinations

Observations*	0	50	100	200	300
#pups(litters) examined	110(8)	111(8)	100(7)	106(7)	73(5)
#pups(litters) affected	0	0	0	0	0

C. DISCUSSION:

1. Maternal Toxicity: Two dams died in the 300 mg/kg/day group and one died in the 200 mg/kg/day group, both as a result of the effects of the test substance. Clinical observations for animals that died included tremors, lost righting reflex, catalepsy, excess salivation, clonic convulsions, labored breathing, bradypnea and decreased motor activity.

   Clinical signs of toxicity were observed in all dose groups. These included: excess salivation ($p \leq 0.05$ to $p \leq 0.01$ at 50 mg/kg/day and above) and tremors ($p \leq 0.01$ at 100 mg/kg/day and above). No other treatment-related clinical signs of toxicity were observed. There were no other treatment-related effects on the dams.

2. Developmental Toxicity:

   a. Deaths/Resorptions: There were no treatment-related increases in either fetal deaths or resorptions.

   b. Altered Growth: There were no indications of increased altered growth in any of the treated groups.

   c. Developmental Anomalies: There were no indications of increased developmental anomalies in any of the treated groups.

   d. Malformations: There were no indications of increased malformations in any of the treated groups. However, it is observed that full visceral and skeletal examinations were not conducted on these animals.

D. Study Deficiencies: None for a range-finding study.

E. Core Classification: Core Supplementary Data.

Maternal NOEL = Close to 50 mg/kg/day
Maternal LOEL = 100 mg/kg/day
Developmental Toxicity NOEL = 300 mg/kg/day (HDT)

Reviewed By: Pamela Hurley, Ph.D. Pamela M. Hurley 12/2/91
Section I, Tox. Branch (H7509C)
Secondary Reviewer: Roger L. Gardner, Head Roger Gardner 12-3-91
Section I, Tox. Branch (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Teratology - Developmental Toxicity (83-3)

SPECIES: Rat

TOX. CHEM. NO./CASWELL NO.: 025B

ACCESSION NUMBER/MRID NO.: 412258-03

TEST MATERIAL: Pynamin Forte

SYNONYMS: D-cis/trans allethrin

STUDY NUMBER(S): KT-91-0094

REPORT NUMBER: Argus 1119-004

SPONSOR: Sumitomo Chemical Company, Ltd., Osaka, Japan

TESTING FACILITY: Argus Research Laboratories, Inc., Horsham, PA

TITLE OF REPORT: Teratology Study in Rats With Pynamin Forte

AUTHOR(S): A.M. Hoberman

REPORT ISSUED: July 17, 1989

CONCLUSION: Pynamin Forte was tested for potential to induce developmental toxicity in rats at the following dose levels: 0, 10, 30 and 100 mg/kg/day. The maternal NOEL was 30 mg/kg/day and the maternal LEL was 100 mg/kg/day (excess salivation and tremors and a decrease in mean body weight gain during days 6-9 of gestation when compared to the control group). The NOEL for developmental toxicity was 100 mg/kg/day (HDT).

Classification: Core Guideline

Testing Guideline Satisfied: 83-3

A. MATERIALS AND METHODS:

1. Test Compound(s)

Chemical Name: 36.5% allyl homolog of cinerin I and 55.5% other allethrin stereoisomers

Description: Amber colored liquid
Batch #(s), Other #(s): Lot # 50310
Purity: 93.4%
Source: Sumitomo Chemical Co., Ltd.
Vehicle (if applicable): aqueous 0.5% (w/v) methylcellulose

2. Test Animals)

Species and Strain (sexes): Male and female Crl:CD®(SD)BR rats.
Age: 71 days (F), 73 days (M) at receipt.
Weight(s): 185-237 g (F), 247-276 g (M), at receipt.
Source(s): Charles River Breeding Laboratories, Inc., Raleigh, NC.

3. Study Design:

This study was designed to assess the developmental toxicity potential of Pynamin Forte when administered by gavage to rats on gestation days 6 through 15, inclusive.

a. Mating:

Natural or artificial insemination? Natural
Describe technique used: Each female rat was placed in cohabitation for up to 4 days with a male rat and was examined daily for presence of spermatozoa in vaginal lavages or a copulatory plug. The day evidence of mating was found was designated as day 0 of presumed gestation.

b. Group Arrangement:

Test Group	Dosage (mg/kg/day)	Pynamin Forte Concentration (mg/ml)	Dosage Volume (ml/kg)	No. Assigned
I	0	0	5	25
II	10	2	5	25
III	30	6	5	25
IV	100	20	5	25

c. Dosing:

All doses were in a volume of 5 ml/kg of body weight/day. Dosing was based on day 6 gestation day body weight.

1) Basis For Selection of Dose Levels: Based on range-finding study (deaths and clinical signs at 200 and 300 mg/kg/day).

2) Preparation: The appropriate amount of the test chemical was weighed out and a sufficient amount of vehicle was added to achieve a total weight of 80 g. The container was capped, shaken and stirred, and allowed to stand to allow air bubbles to dissipate. The resulting suspensions were stirred again prior to dosing.

3) Frequency of Preparation: Daily.

4) Storage Conditions: The test substance was kept in a cool, dry, well ventilated area and protected from heat and flame.

5) Stability Analyses: Stability of the test substance was on file with the Sponsor and was not provided in the report.

6) Homogeneity Analyses: Conducted on the lowest and highest concentrations used in this study, as well as some other studies, ranging from 2 mg/ml to 100 mg/ml. Samples were taken from the top, middle and bottom of the sample mixture.

7) Concentration Analyses: One 10 gm sample of each prepared batch was reserved on the first day and the last day of test substance preparation. Three additional 10 g samples

from the 2 mg/ml concentration were reserved as well. The samples taken from each concentration were sent to Lancaster Laboratories, Lancaster, PA for analyses.

d. Maternal Examinations

1) Clinical Observations and Mortality: All female rats were observed for appearance, toxic effects, moribundity and/or mortality and general behavior at least twice daily during the dosage and postdosage periods of the study.

2) Body Weight Determinations: Maternal body weights were recorded twice prior to initiation of cohabitation, on day 0 of presumed gestation and then daily during the dosage and postdosage periods.

3) Food Consumption: Food consumption was recorded daily for each day of the dosing and postdosing periods (days 6 - 20 of presumed gestation).

4) Gross Necropsy:

Animals which died or were sacrificed in moribund condition prior to end of exposure period and were subjected to complete gross pathological examinations: The report had no statement on animals that died prior to the end of the exposure period. However, no animals died during the exposure period.

Animals sacrificed at the end of the treatment/observation period which were subjected to complete gross pathological examinations: All dams. All gross lesions were preserved in formalin for possible future evaluation.

5) Uterine Examinations: The following observations were recorded:

Number of corpora lutea
Number of live fetuses
Number of dead fetuses
Early and late resorptions
Total implantations
Individual fetal weights

e. Fetal Examinations:

The fetuses were examined in the following manner: The fetuses were removed from the uterus and individually identified. Every fetus was sexed, weighed and examined for external abnormalities. Approximately one-half of the fetuses from each litter were examined for soft tissue alterations using a variation of Wilson's sectioning technique. The remaining fetuses in each litter were eviscerated, cleared, stained with alizarin red S and examined for skeletal alterations.

f. Historical Control Data:

Historical control data were provided to allow comparison with concurrent controls.

g. Statistical analysis:

The following statistical analysis methods were employed: parametric and nonparametric tests. These include Bartlett's (test for homogeneity of variance), analysis of variance (ANOVA - for homogeneous data), Dunnett's (if ANOVA significant), Kruskal-Wallis (nonparametric, not including proportion data, <= 75% ties), Dunn's test (if Kruskal-Wallis test is significant), Fisher's exact test for > 75% ties, variance test for homogeneity of the bionomial distribution (proportion data), analysis of covariance and covariance analyses t-test.

h. Compliance:

A signed Statement of Confidentiality Claim was provided (only on the basis of its falling within the scope of FIFRA). The document is considered to be confidential and trade secret information in all other countries and for all purposes other than those enunciated in FIFRA.

A signed Statement of compliance with EPA GLP's was provided (prior to GLP's).

B. RESULTS:

1. Dosage Preparation: For the 30 and 100 mg/kg/day dose levels, the suspension concentrations were within +/- 10%. For the 10 mg/kg/day dose level, the first day dose concentration was 103% above the target, but the last day dose concentration was 64% of the target. Based on these results, samples from this dose level were analyzed form 3 addional days. These values were within 87-102% of the target. Therefore, the actual concentrations were acceptably close to the target concentrations.

   Testing of the homogeneity samples resulted in an average relative standard deviation of 2.38% for the 2.0 mg/ml level, 5.5% for 3.0 mg/ml, 1.1% for 5.0 mg/ml, 8.56% for 60.0 mg/ml, 2.02% for 80.0 mg/ml and 1.03% for the 100 mg/ml level. The samples were acceptably homogeneous.

2. Maternal Toxicity

   a. Clinical Observations and Mortality: No deaths were observed during the study. Statistically significant clinical signs of toxicity were observed in the 100 mg/kg/day group when compared to controls. These included excess salivation and tremors. Non-statistically significant, but attributed to the test substance included body jerks, chromodacryorrhea and/or oral exudate, also seen in the high dose group. No other treatment-related clinical signs of toxicity were observed. Non-treatment-related signs included a lesion on the head (1 high dose dam) and local areas of alopecia (all groups, including controls).

   b. Body Weight Determinations: A statistically significant decrease in mean body weight gain was observed in the high dose group during days 6-9 of gestation, when compared to the control group. This decrease in body weight gain was mainly from a large decrease in body weight gain between days 6-7. In addition, between days 6 and 7, a significant decrease in body weight gain was observed in the mid-dose group. This did not significantly affect the body weight gain for this dose group from days 6-9. During the post-dosing period, the mean body weight gain for the high dose group was comparable to controls. No other

statistically significant differences between the treated and control groups were observed.

The investigators supplied the following data:

Table I: Body Weight Gains (grams)[a]

Group:	Days 0 - 6	Days 6 - 9	Days 6 - 16	Days 16 - 20	Days 0 - 20
Control	42.5	16.7	71.1	69.6	183.2
10	45.0	16.7	71.9	71.4	188.3
30	43.8	15.3	71.9	71.6	187.3
100	43.4	12.9*	67.8	71.0	182.2

a = Data extracted from (study or report number Argus 1119-004 and table 4)
* = Significantly different from controls ($p<=0.01$).

c. Food Consumption: No treatment-related differences in food consumption were observed in any of the treated groups when compared to controls for any time period.

d. Gross Pathology:

Necropsy observations included hydrometra (bilateral, slight) of the uterus in 1 high dose female (not pregnant) and large placentas in 1 low dose and in 1 mid-dose dam. No other observations were noted in the report.

e. Caesarean Section Observations: No treatment-related differences when compared to controls were observed in pregnancy incidences, mean values for corpora lutea, implantations, implantation efficiencies, litter sizes, live and dead fetuses, early and late resorptions, fetal body weights, fetal sex ratios, or fetal viability. The following table summarizes the observations.

Table III: Caesarean Section Observations[a]

	Control	LDT	MDT	HDT
Dose: mg/kg/day	0	10	30	100
#Animals Assigned	25	25	25	25
#Animals Mated/Inseminated	25	25	25	25
Pregnancy Rate (%)	25(100)	24(96)	24(96)	22(88)
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	0	1	1	3
#Aborted	0	0	0	0
#Premature Delivery	0	0	0	0
Corpora Lutea/dam	18.7	17.5	18.2	17.9
Total Implantation	410	391	396	355
Implantations/Dam	16.4	16.3	16.5	16.1
Implantation Efficiency (%)[b]	88.8	93.2	91.1	90.5
Litter Size/Dam	15.0	15.4	15.4	15.3
Total Live Fetuses	375	371	370	336
Live Fetuses/Dam	15.0	15.4	15.4	15.3
Total Resorptions	35	20	26	19
Early	34	20	26	19
Late	1	0	0	0
Resorptions/Dam	1.4	0.8	1.1	0.9
Dams With Any Resorptions	17	11	14	11
Dams With Viable Fetuses	25	24	24	22
Total Dead Fetuses	0	0	0	0
Mean Fetal Weight (gm)	3.65	3.68	3.58	3.60
Sex Ratio (% Male)	52.7	50.0	52.8	50.6

[a] = Data extracted from (study or report number Argus 1119-004 and tables 7 and 8)

[b] = Implantation efficiency is the number of implantation sites divided by the number of corpora lutea multiplied by 100.

3. Developmental Toxicity: No treatment-related alterations (malformations or variations) were observed in any of the treated groups when compared to controls. The following tables summarize some of the alterations observed.

Table IV: External Examinations

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups(litters) examined	375(25)	371(24)	370(24)	336(22)

No gross external alterations were observed.

Table V: Visceral Examinations

Observations[+]	Control	Low Dose	Mid Dose	High Dose
#pups(litters) examined	179(25)	180(24)	178(24)	164(22)
#pups(litters) affected	0(0)	1(1)	2(1)	0(0)
Brain				
Lateral and third ventricles, slightly dilated	0(0)[a]	0(0)	2(1)	0(0)
Kidneys				
Pelvis, slightly dilated.	0(0)	1(1)	0(0)	0(0)

([+]) some observations may be grouped together
([a]) fetal [litter] incidence

Table VI: Skeletal Examinations

Observations*	Control	Low Dose	Mid Dose	High Dose
#pups(litters) examined	196(25)	191(24)	192(24)	172(22)

The following tables taken directly from the study report summarize the skeletal alterations that were observed in this study.

TABLE 12 (PAGE 1): SUMMARY OF FETAL SKELETAL ALTERATIONS
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 6-15 of Gestation)			
		0(Vehicle)	10	30	100
Litters Evaluated	N	25	24	24	22
Fetuses	N	196	191	192	172
Live	N	196	191	192	172
Dead	N	0	0	0	0
Litters with fetuses with skeletal malformations	N(%)	1(4.0)	0	0	0
Litters with fetuses with skeletal Variations	N(%)	9(36.0)	4(16.7)	5(20.8)	4(18.2)
Fetuses with skeletal malformations	N(%)	1(0.5)	0	0	0
Fetuses with skeletal variations	N(%)	13(6.6)	5(2.6)	7(3.6)	4(2.3)
VERTEBRAE:					
Thoracic, Arch, Hemivertebra (M)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Thoracic, Centra, Unilateral Ossification (M)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Thoracic, Centra, Not Ossified (M)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Thoracic, Centrum, Bifid (V)					
Litter Incidence	N(%)	2(8.0)	0	0	0
Fetal Incidence	N(%)	3(1.5)	0**	0**	0**

TABLE 12 (PAGE 2): SUMMARY OF FETAL SKELETAL ALTERATIONS
(See footnotes on the last page of this table.)

		Dosage Group (mg/kg/days 6-15 of Gestation)			
		0(Vehicle)	10	30	100
Litters Evaluated	N	25	24	24	22
Fetuses	N	196	191	192	172
Live	N	196	191	192	172
Dead	N	0	0	0	0
RIB(S):					
Cervical Rib Present (V)					
Litter Incidence	N(%)	2(8.0)	0	0	0
Fetal Incidence	N(%)	2(1.0)	0	0	0
Fused (M)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b]	0	0	0
Wavy (V)					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)	0	0	0
DELAYED STERNAL OSSIFICATION (Summary of incompletely ossified manubrium and incompletely or not ossified 1st sternal center)					
Litter Incidence	N(%)	5(20.0)	3(12.5)	5(20.8)	3(13.6)
Fetal Incidence	N(%)	5(2.6)[a,b]	4(2.1)	7(3.6)	3(1.7)
Manubrium:					
Incompletely Ossified (V)					
Litter Incidence	N(%)	2(8.0)	0	0	0
Fetal Incidence	N(%)	2(1.0)[a,b]	0	0	0
Sternal Centers					
1st. Incompletely Ossified (V)					
Litter Incidence	N(%)	4(16.0)	2(8.3)	3(12.5)	1(4.5)
Fetal Incidence	N(%)	4(2.0)[a]	2(1.0)	3(1.6)[a]	1(0.6)
1st. Not Ossified (V)					
Litter Incidence	N(%)	1(4.0)	2(8.3)	2(8.3)	2(9.1)
Fetal Incidence	N(%)	1(0.5)[b]	2(1.0)	4(2.1)[d,e,f]	2(1.2)

TABLE 12 (PAGE 3): SUMMARY OF FETAL SKELETAL ALTERATIONS

		Dosage Group (mg/kg/days 6-15 of Gestation)			
		0(Vehicle)	10	30	100
Litters Evaluated	N	25	24	24	22
Fetuses	N	196	191	192	172
Live	N	196	191	192	172
Dead	N	0	0	0	0
DELAYED PELVIC OSSIFICATION (Summary of incompletely ossified and not ossified Pubes and/or ischia)					
Litter Incidence	N(%)	3(12.0)	1(4.2)	2(8.3)	1(4.5)
Fetal Incidence	N(%)	3(1.5)[b]	1(0.5)	4(2.1)[f]	1(0.6)
Pubes, Incompletely Ossified					
Litter Incidence	N(%)	3(12.0)	1(4.2)	1(4.2)	1(4.5)
Fetal Incidence	N(%)	3(1.5)[b,c]	1(0.5)	1(0.5)[g]	1(0.6)
Ischia, Incompletely Ossified					
Litter Incidence	N(%)	1(4.0)	0	0	0
Fetal Incidence	N(%)	1(0.5)[b,c]	0	0	0
Pubes, Not Ossified					
Litter Incidence	N(%)	0	0	1(4.2)	0
Fetal Incidence	N(%)	0	0	3(1.6)[d,e,f]**	0

M = Malformation, V = Variation.
a. Fetus 3201-9 also had other skeletal alterations.
b. Fetus 3210-12 also had other skeletal alterations.
c. Fetus 3218-3 also had other skeletal alterations.
d. Fetus 3251-1 also had other skeletal alterations.
e. Fetus 3251-5 also had other skeletal alterations.
f. Fetus 3251-7 also had other skeletal alterations.
g. Fetus 3274-1 also had other skeletal alterations.
** Significantly different from the vehicle control value ($P<0.01$).

TABLE 13 (PAGE 1): FETAL OSSIFICATION SITES (LIVEBORN FETUSES - DAY 20)

		Dosage Group (mg/kg/days 6-15 of Gestation)			
		0(Vehicle)	10	30	100
Litters Examined	N	25	24	24	22
Fetuses Examined	N	196	191	192	172
Ossification Sites/Litter					
Hyoid	$\bar{X}$±S.D.	0.87 ± 0.19	0.87 ± 0.21	0.91 ± 0.14	0.90 ± 0.16
Cervical (VERTEBRAE)	$\bar{X}$±S.D.	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00	7.00 ± 0.00
Thoracic (VERTEBRAE)	$\bar{X}$±S.D.	13.24 ± 0.21	13.18 ± 0.27	13.19 ± 0.22	13.34 ± 0.30
Lumbar (VERTEBRAE)	$\bar{X}$±S.D.	5.76 ± 0.21	5.80 ± 0.26	5.80 ± 0.22	5.66 ± 0.31
Sacral (VERTEBRAE)	$\bar{X}$±S.D.	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00	3.00 ± 0.00
Caudal (VERTEBRAE)	$\bar{X}$±S.D.	4.84 ± 0.52	4.94 ± 0.36	4.75 ± 1.06	4.77 ± 0.54
Ribs	$\bar{X}$±S.D.	13.19 ± 0.16	13.15 ± 0.22	13.14 ± 0.17	13.27 ± 0.26
Manubrium (STERNUM)	$\bar{X}$±S.D.	1.00 ± 0.00	1.00 ± 0.00	1.00 ± 0.00	0.99 ± 0.04
Sternal (STERNUM)	$\bar{X}$±S.D.	3.83 ± 0.16	3.84 ± 0.25	3.65 ± 0.61	3.84 ± 0.22
Xiphoid (STERNUM)	$\bar{X}$±S.D.	0.99 ± 0.04	0.99 ± 0.04	0.95 ± 0.21	1.00 ± 0.00
Forepaws					
Carpals	$\bar{X}$±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Metacarpals	$\bar{X}$±S.D.	3.37 ± 0.28	3.63 ± 0.30	3.52 ± 0.33	3.53 ± 0.34
Digits	$\bar{X}$±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
Phalanges	$\bar{X}$±S.D.	5.00 ± 0.20	5.02 ± 0.21	4.84 ± 1.05	5.04 ± 0.34
Hindpaws					
Tarsals	$\bar{X}$±S.D.	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Metatarsals	$\bar{X}$±S.D.	4.00 ± 0.00	3.99 ± 0.04	3.96 ± 0.20	4.00 ± 0.00
Digits	$\bar{X}$±S.D.	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00	5.00 ± 0.00
Phalanges	$\bar{X}$±S.D.	4.83 ± 0.47	4.88 ± 0.31	4.60 ± 1.07	4.82 ± 0.56

C. DISCUSSION:

1. Maternal Toxicity: Statistically significant clinical signs of toxicity were observed in the 100 mg/kg/day group when compared to controls. These included excess salivation and tremors. In addition, a statistically significant decrease in mean body weight gain was observed in the high dose group during days 6-9 of gestation, when compared to the control group.

2. Developmental Toxicity: There were no treatment-related developmental toxicity observations in this study at any dose level tested.

D. Study Deficiencies: There were no major deficiencies in study design and conduct.

E. Core Classification: Core Guideline Data.

Maternal NOEL = 30 mg/kg/day
Maternal LOEL = 100 mng/kg/day
Developmental Toxicity NOEL = 100 mg/kg/day (HDT)

END